

Actinomycetoma by *Actinomadura madurae*: Clinical Characteristics and Treatment of 47 Cases

Abstract

Context: Mycetoma is a chronic, granulomatous disease caused by fungi (eumycetoma) or aerobic filamentous actinomycetes (actinomycetoma). *Actinomadura madurae* is one of the most frequent actinomycetes. **Aim:** The study aims to provide an update on clinical, diagnostic, therapeutic, and outcome data for patients with actinomycetoma in a single center in Mexico. **Settings and Design:** This was a retrospective study of 47 cases diagnosed with actinomycetoma. **Subjects and Methods:** The cases were selected from a total of 536 mycetoma obtained during 35 years (from 1985 to 2019). Clinical data were retrieved from the clinical records of our department. Microbiological data were obtained from our Mycology laboratory. **Statistical Analysis:** Frequencies and percentages were used for categorical variables. Normality was determined with the Kolmogorov–Smirnov test. We used means and medians to describe the variables. **Results:** Forty-seven patients with actinomycetoma were included; female:male ratio 1.9:1; median age 38 years. The foot was the most affected region in 76.5% of cases. The bone invasion was observed in 89%. The time between symptoms onset and diagnosis was 5.5 years. Grain detection by direct examination was positive in 95% of cases. The most commonly used, as well as the most effective treatment scheme was streptomycin + sulfamethoxazole-trimethoprim with dapsone. Sixty-three percent (30 patients) achieved clinical and mycological cure, and 10.6% (5 patients) had treatment failure. **Conclusions:** We highlight the importance of designing therapeutic strategies to standardize treatments and gain more experience to improve the care of these patients.

Keywords: *Actinomadura madurae*, actinomycetoma, mycetoma, osteolysis, streptomycin, sulfamethoxazole/trimethoprim

Introduction

Mycetoma is a chronic, neglected, granulomatous disease due to traumatic implantation of microorganisms and characterized by firm nodules, with multiple fistulous sinus tracts draining serous or purulent material containing the etiological agent.^[1,2] Mycetoma may be related to filamentous fungi (eumycetoma) or aerobic filamentous actinomycetes (actinomycetoma).^[1] It is frequent in low-income countries mostly in the so-called “mycetoma belt,” close to the Tropic of Cancer (between latitude 15° south and 30° north), in regions of subtropical and tropical dry climate.^[1,2] Sudan (>6000), Mexico (>4000), and India (approximately 2000) report the majority of cases.^[3] In Mexico, actinomycetoma is observed in 92%–96% of all cases of mycetoma; *Nocardia brasiliensis* accounts for 66%–85% of cases

of actinomycetoma, and *Actinomadura madurae* for 8%–10%.^[3-5]

Actinomycetoma due to *A. madurae* is clinically indistinguishable from eumycetomas [Table 1]; however, the first one is more aggressive, rapidly progressive, and tends to be unstable when compared with eumycetoma. The primary clinical topography includes the lower limbs, particularly the feet presenting with a painless swelling and tumefaction, with a mild exudative process and fistulas, developing gruesome deformity. It is more aggressive than eumycetoma, with bone involvement, including periostitis, bone erosion, or cavitation.^[6] In general, actinomycetoma has a male predominance, mainly due to outdoor, occupational activities (farmers, agricultural workers).^[4]

Actinomycetoma therapy is based on long-term antibiotics with variable

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Table 1: Comparative characteristics between eumycetoma and actinomycetoma due to *Actinomadura madurae*

	Eumycetoma	Actinomycetoma
Etiologic agent	Black or white fungus	Filamentous bacteria
Geography	Common in Africa and India	Common in Latin America, India, and Iran
Major risk groups	Field workers	Field workers
Age group	Common in 20–40 years	Common in 20–50 years
Site of lesion	Usually feet	Usually feet and leg
Type of lesion	Limited extension	Diffuse
Sinus tracts	Few	Few
Grain color and size	Often visible, black or white	Often visible, predominantly white.
Disease evolution	Slow and progressive	Slow and progressive
Bone involvement	Late	Early
Osteolysis	Few and large cavities	Few and large cavities
Treatment	Systemic antifungal	Combined antibiotics and antiinflammatories.
Surgery	Effective	Not indicated

results; moreover, current treatment guidelines are scarce and mainly based in case series or individual case reports.^[4,6]

Subjects and Methods

This was a retrospective study of 47 cases diagnosed with actinomycetoma by direct grain examination (KOH and Lugol), histopathology, culture (Lowenstein-Jensen media, and Saboraud-dextrose agar), biochemical tests by standardized methods (ATB Vitek® from Biomérieux) and PCR with partial sequencing of the 16S rRNA.^[1,7] The cases were selected from a total of 536 mycetoma obtained during 35 years (from 1985 to 2019); actinomycetoma by *A. madurae* represented 8.7% of the cases. Clinical data were retrieved from the clinical records of our department. Microbiological data were obtained from our Mycology laboratory. Histopathologic examination reported grains in 21 cases (44.7%).

Statistical analyses

Statistical analyses were performed with SPSS version 25 (NY, USA). Frequencies and percentages were used for categorical variables. Normality was determined with the Kolmogorov–Smirnov test. We used means and medians to describe normally and nonnormally distributed variables, respectively.

Results

A total of forty-seven patients with actinomycetoma were analyzed; 31 females (66%) and 16 males (34%; ratio 1.9:1) aged between 17 and 62 years (median 38, mean 38.5). The demographic, clinical, and diagnostic data is presented in [Table 2].

Most subjects were housewives (31 cases, 66%), followed by farmer/agricultural workers (10 cases, 21%).

With regard to the actinomycetoma lesion site, the foot was the most involved site in 36 cases (76.5%) [Figure 1]. The

bone involvement was documented in 42 cases (89.4%), developing periostitis, osteitis, osteofibrosis, and osteolysis with cavitation. The time between symptoms onset and diagnosis was 5.5 years (range: 3 months to 20 years). Thirty-two patients (68%) presented itching and moderate pain on palpation, while fifteen patients (32%) reported no symptoms associated with the disease. Symptoms reverted during actinomycetoma treatment without requiring additional treatment.

Direct examination detected grains in 45 cases (95.7%). *A. madurae* grew in 35 cases (74.5%) with culture with a swab [Figure 2]. Histopathological analysis demonstrated grains in 21 patients (44.68%). Twelve culture isolates were identified to species level using nucleotide sequencing of 16S rRNA PCR analysis.

Various treatment schemes were used; conventional regimen with streptomycin (IM) 1 g every third day (3 g weekly) up to a maximum of 50 g plus sulfamethoxazole-trimethoprim (SMX-TMP) 800 mg/160 mg every 12 h, continuing with SMX-TMP plus DDS 100 mg/day was used in 28 patients (59.5%). Eleven patients (23.4%) were treated with SMX-TMP plus dapsone; streptomycin 1 g IM every third day (3 g weekly) up to a maximum of 50 g plus SMX-TMP 800 mg/160 mg every 12 h, continuing with SMX-TMP plus ciprofloxacin 500 mg every 12 h was used in six patients (12.7%). In two cases (4.2%), rifampicin, SMX-TMP, and dapsone were used.

Thirty patients (63.8%) achieved clinical and microbiological cure, and twelve cases (25.5%) reached disease improvement. Five patients (10.6%) had treatment failure and were lost on follow-up. In 8 patients (17%), there was loss of function, with significant disability. The criterion for response to treatment was clinical and microbiological improvement (biopsy or direct examination).

The streptomycin dose was 50 g total, which is equivalent to approximately 4 months of treatment. Streptomycin adverse events like renal disease or hypoacusis were not



Figure 1: Actinomycetomas due to *A. madurae*. (a) Extensively affecting the ankle, developing an inflammatory and fibrous tumefaction with few fistulas. (b) Extensive fistulous presentation in the abdomen. (c) In hand with mild induration and fistulas

reported or warrant discontinuation. The total treatment duration ranged between 14 months and 18 years (median: 26 months); however, the duration was adapted according to disease response to treatment (clinical and microbiological outcome) and bone involvement severity.

Discussion

Actinomadura madurae is a cosmopolitan microorganism, commonly isolated in dry and often tropical areas; it is estimated that they represent a little more than 10% of all cases. The majority of reports come from Asia, mostly India (31%) and Iran; in Africa, including Morocco and Tunisia; in Europe, from Romania and Bulgaria and in America, from Mexico, Venezuela, and Argentina. Its name comes from the first cases of mycetoma in the Madurai region of southern India.^[1,3,6]

In our study, we observed actinomycetomas due to *A. madurae* in 8.7% of mycetoma, similar to previous studies.^[3,6] The average age was 38 years. The male to female ratio in our series was 1:1.9, similar to a case-series from Tunisia reporting a male to female ratio of 1:1.5,^[8] however, different from several studies pointing male predominance for actinomycetoma.^[4,5,9] Outdoor activities may influence this trend, and also the host genetic variation to susceptibility to actinomycetoma,^[10] as well as the hormonal levels, since estrogens may protect against this disease, while progesterone and testosterone may cause proinflammatory response.^[11] Most of our female patients were housewives; however, they may perform additional, outdoor activities that may increase the risk of infection. Most of our cases came from the central zone of the country, with warm-dry to warm-humid climates (Guanajuato, State of Mexico and Michoacán), with an average 250–500 mm/year rainfall and a temperature above 20°C.

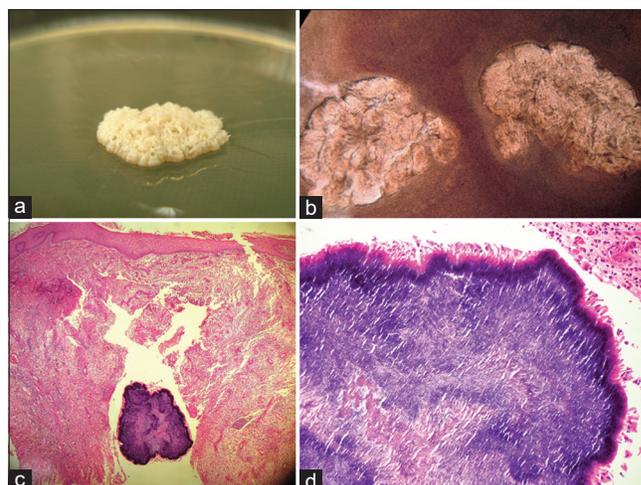


Figure 2: Microbiological aspects of *A. madurae*. (a) Culture in Sabouraud medium, cerebriform colony. (b) Grains on direct examination (Lugol, 5×). (c) Biopsy with granulomatous process and basophilic grain at biopsy (H and E, 10×). (d) Close-up of the grain, observed at the periphery with filament fringe (H and E, 40×)

The median lag time between symptom onset and diagnosis was 5 years; most cases were in advance stages limiting the therapeutic outcome, following previous studies.^[4,6]

The main affected region was in the lower limbs, on the foot (76.5%) and the leg (8.5%), similar to eumycetoma; few cases arise in the upper limbs, and trunk (2.1%); however, previous studies in Mexico reported that trunk location was up to 19% of cases,^[4,5] mainly due to implantation with plant debris and wood.

Clinically, most cases presented as increased volume and deformity of the region, with few fistulae; few cases were cryptic, hardening the diagnosis. In two cases, clinical manifestations were mild, called mini-mycetoma and were observed in two youngest patients (17 and 19 years old); this uncommon clinical type is often found in adolescents and young adults.^[4]

Bone invasion was reported in 90% of cases, developing periostitis, osteitis, osteofibrosis, and partial (forming geodes or cavities) or complete osteolysis. The severity of bone involvement is directly related to the response to treatment; TMP/SMX is an excellent option since adequately penetrates the bone tissue.^[4,12]

In our study, the observation of grains on direct examination was detected in 95% of cases. *A. madurae* grains are constituted by thin filaments (1 μm), the grains often visible to the naked eye; grains measured between 0.5 and 5 mm, yellowish-white colored, irregular round shape and soft consistency. Microscopically, lobes with outer filament fringes are usually observed; *A. madurae* grains differ from *Actinomadura pelletieri* that are red-colored, and *Streptomyces somaliensis* showing hard consistency grains. Cultures grew in 75% of cases, probably due to the compactness of the grains, covered with cementitious

Table 2: Characteristics of the study population

	N=47 (%)
Age, mean±SD, years (Range)	38.5±11.83 (17–62 years).
Gender, female/male (%)	31 (66)/16 (34)
Occupation (%)	
Housewife	31 (66)
Farmer/agricultural worker	10 (21)
Factory worker	5 (11)
Construction worker	1 (2)
Time between symptoms onset and diagnosis, mean±SD, years (range)	5.5±4.3 (3 months–20 years)
Affected region (%)	
Foot	36 (76.5)
Leg	4 (8.5)
Hand	3 (6.3)
Arm	2 (4.2)
Chest	2 (4.2)
Back	1 (2.1)
Foot/groin	1 (2.1)
Bone invasion (%)	
No activity	5 (10.6)
Osteolysis and cavitation	42 (89.4)
Direct microscopic examination, positive grains (%)	45 (95.7)*
Culture, positive/negative (%)	35 (74.5)/12 (25.6)
Histopathologic examination, positive grains (%)	21 (44.68)
Treatment outcome (%)	
Cure	30 (63.8): 22 STM+TMP/SMX+DDS; 3 TMP/SMX+DDS; 5 STM+TMP/SMX+CIP.
Improvement	12 (25.5): 5 TMP/SMX+DDS; 5 STM+TMP/SMX+DDS; and 2 TMP/SMX+DDS+RIF.
Failure	5 (10.6): 3 TMP/SMX+DDS; and 1 STM+TMP/SMX+DDS; and 1 STM+TMP/SMX+CIP

SD=Standard deviation; *One case had two etiologic agents: *N. brasiliensis*+*A. madurae*; STM: Streptomycin; TMP/SMX: Sulfamethoxazole-trimethoprim; DDS: Dapsone; CIP: Ciprofloxacin; RIF: Rifampicin

substances, not allowing *in vitro* development of actinomycete, similar to *S. somaliensis*, but contrary to *Nocardia* spp. and *A. pelletieri*, which are isolated in most cases. Cultures of *A. madurae* grow slowly between 20 and 40 days, at 37°C; first isolation is often difficult; grains need to be fragmented and cleaned in sterile saline before sowing. The colonies are usually small, limited, yellowish-white colored, moist, smooth in consistency, slightly acuminate, and often in a cerebriform fashion. *A. madurae* is a Gram-positive, non-acid-alcohol-resistant

microorganism forming septate filaments (1 µm), and fragmenting in coccoid and bacillary forms, with round or elliptical spores.^[1,4]

Histopathologic analysis showed chronic suppurative granuloma with variable hyperkeratosis, irregular acanthosis, and pseudoepitheliomatous hyperplasia, accompanied by an intense inflammatory infiltrate, often developing microabscesses of polymorphonuclear cells, with macrophages, plasma cells, and lymphocytes. *A. madurae* grains are large, basophilic, not uniformly stained, with a pale center and eosinophilic fringe.^[1,13]

No therapeutic guidelines are available, and the treatment of actinomycetoma usually requires a combination of drugs; monotherapy is not recommended. Long-term (>1 year) multidrug treatment is the most commonly used with variable response. Several schemes, including streptomycin, TMP/SMX, diamino diphenyl sulfone, have been tested. Other therapeutic options include rifampicin, isoniazid, doxycycline, and amikacin with individual therapeutic success.^[7,12] We suggest the use of streptomycin (up to 50 g total) with TMP/SMX, followed by ciprofloxacin maintained for at least 1 year; surgical debridement is not routinely suggested since may spread or relapse the infection.^[1,6,12]

In our study, a clinical and mycological cure was achieved in 60% of cases; 25% showed clinical improvement, and up to 10% failed to treatment or worsened. According to our results and other experiences, the therapy of actinomycetoma by *A. madurae* is difficult and often complicated with bone invasion. *In vitro* studies have shown promising activity with oxazolidone (DA-7867) and quinolones (gatifloxacin and moxifloxacin, and garenoxacin);^[14] however, the cost and treatment duration limit their extensive use; therefore, the therapy proposed in our study is relevant since it is effective in most cases and affordable.

Limitations of our study include the retrospective, single-center design, the multiple treatment regimens used, and the small sample size. Since these cases were selected from a single-center, this may not accurately represent the cases in Mexico.

Herein, we reported 47 actinomycetoma cases due to *A. madurae* in a tertiary-level Hospital in México. Most cases had late presentations with severe complications and variable therapeutic results. Early diagnosis may evade gruesome complications and bone affection, improving the response to long-term multidrug treatments. We highlight the importance of designing strategies to standardize treatments and gain more experience to improve the care of these patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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